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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/389,835	09/03/1999	ARNOLD E. RUOHO	96429/9079	5941

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EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	19

DATE MAILED: 10/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/389,835	Ruoho et al.
Examiner	**Art Unit**
Michael Brannock, Ph.D	1646

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 2, 2002*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2-28* is/are pending in the applica

4a) Of the above, claim(s) *13, 14, and 19-28* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-12 and 15-18* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 15, 2/13/02, have been entered in full.

2. Claims 2-28 are pending. Claims 2-12, 15-18 will be examined to the extent that the claims relate to the elected species of invention, i.e. a chimeric Bacteriorhodopsin/β2-adrenergic receptor.

Claims 13, 14, 19-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made in Paper No. 18, 7/2/02. As no arguments were presented as to why the restriction requirement might be improper, the election is considered to be made without traverse. The restriction requirement is therefore maintained and made final.

Response to Amendment

3. Applicant is notified that the amendments presented in Paper 15, 2/27/02, have been entered in full.

Withdrawn Rejections:

4. The rejection of claims 1, 6-12 under 35 U.S.C. 112, second paragraph, as set forth in item 4 of Paper 14 is withdrawn in view of Applicant's amendments.

5. The rejection of claims 4 and 5 under 35 U.S.C. 112, first paragraph, as set forth item 6 of Paper 14 is withdrawn in view of the teachings of Kenakin-T, *Pharmacological Reviews* 48(3)413-462, 1996, who teaches that the ability of short peptides, comprising the third intracellular loop of a GPCR, to activate a G-protein appears to be a general property of GPCRs, see the paragraph bridging pages 435 and 436.

6. The rejection of claims 1, 11 and 12 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No: 5641650 as set forth in item 8 of Paper 14 is withdrawn in view of Applicant's amendments.

7.

8. The rejection of claims 4 and 5 under 35 U.S.C. 103(a) as being unpatentable over Popot *et al.*, *Current Opinion in Biotechnology* 6:394-402, 1999 and Hoflack *et al.*, *Trends in Pharm. Sci.* 15:7-9, 1994, in view of Shi *et al.*, *J. Biol. Chem.* 270(5)2112-2119, 1995, as set forth in item 11 is withdrawn in view of Applicant's persuasive arguments.

New Rejections:

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 2-12, 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Popot *et al.*, *Current Opinion in Biotechnology* 6:394-402, 1995, Hoflack *et al.*, *Trends in Pharm. Sci.* 15:7-9, 1994 and Teufel *et al.*, *EMBO Journal, 12(9)3399-3408, 1993*, in view of Okamoto *et al.*, Cell 67(723-730)1991.

Popot *et al.* teach that chimeric constructs of bacteriorhodopsin and of G-protein receptors can be made for the purposes of functional and structural investigations (pg 396 col 1); that bacteriorhodopsin "can be used as a 'bench top' on which to arrange engineered loops that are designed to form binding or catalytic sites (pg 397 col. 2), and that a wealth of data indicates that most of the six loops connecting the transmembrane helices in bacteriorhodopsin can be tampered with to large extents and at least three of them can be cut without preventing refoloding of the proteins (e.g. cytoplasmic loop III, reference 61 Teufel *et al*) (pg 397 col. 2). Further, the use of archaebacterium for recombinant expression of bacteriorhodopsin chimeras is old and well established in the art, as disclosed by Popot et al., (see pg 397, col 2). Further, it is old and well

established in the art that bacteriorhodopsin is famous as a template to construct three dimensional models of G-protein coupled receptors (GPCRs), see Hoflack *et al., Trends in Pharm. Sci.* 15:7-9, 1994, especially col. 1 of page 7. Teufel *et al.* teach that the protein architecture of bacteriorhodopsin (BR) "suggests the possibility of using BR as a structural scaffold in the construction of biological membranes with new and pre-defined properties by replacing the extra-membrane parts of BR with exogenous polypeptide modules of known function", see col 2 of page 3399. Additionally, Teufel et al. teach that the "structural integrity of loops B/C, CD, D/E, and E/F (E/F is the third cytoplasmic loop) is not a prerequisite of BR function and that the construction of multifunctional proteins on the basis of BR as a structural scaffold is a feasible proposition. Loops B/C, CD, D/E and E/F are now clearly identified as prime candidates for future constructions of more complex loop replacements" see the last paragraph of page 3405. Additionally, Teufel *et al.* define what residues are to be considered the third cytoplasmic loop, see Fig 1, which correspond exactly to amino acids 171-179 of the instant SEQ ID NO: 2. Okamoto *et al.* teach that peptides corresponding to the third cytoplasmic loop of a GPCR, e.g. the human β-adrenergic receptor, can activate G- protein, see the Abstract.

Therefore, it would be obvious to one of ordinary skill in the art, with reasonable expectation of success to construct chimeric bacteriorhodopsin/ GPCRs, as taught Popot *et al.* and Teufel *et al.* using regions that are structurally analogous between GPCRs and bacteriorhodopsin, as is well established in the art (see Hoflack et al.), particularly that of the third intracellular loop of the human β-adrenergic receptor as taught by Okamoto *et al.* The

motivation to do so is provided by Popot *et al.* who teach that bacteriorhodopsin "can be used as a 'bench top' on which to arrange engineered loops that are designed to form binding or catalytic sites (pg 397, col 2) and by Okamoto *et al.* who teach the third intracellular loop of the human β-adrenergic receptor provides for binding and activation of G-proteins, and who also teach the need for further study of the structure and function of the third intracellular loop of the human β-adrenergic receptor as is well appreciated in the art, e.g. see Introduction and Discussion. Further, the construction of a bacteriorhodopsin chimera at amino acids 171-179 (intracellular loop III) is suggested by Teufel who show these residues to define the cytoplasmic loop III, see Figure 2.

Applicant's arguments, as the arguments may relate to this rejection, are addressed below. Applicant is correct in pointing out that Popot et al. was published in 1995. Applicant argues that at page 395, col 2, Popot is merely referring to experiments showing assembly of fragments of membrane proteins. This argument has been fully considered but not deemed persuasive. This passage was referred to by the examiner to provide an indication of what is known of the versatility of the bacteriorhodopsin system and of the ability of the receptor to accommodate analogous portions from entirely different receptors. In this section, Popot teach that the "split protein" chimera approach can be used as an alternative to the construction of traditional chimeras, but it would be obvious to one of ordinary skill in the art that Popot et al. is extolling the advantages of the chimeric approach, in general, to structure/function analysis of receptors.

Applicant argues that neither Popot nor Hoflack provide the particular motivation to use the third extracellular loop. Okamoto *et al.* provide the motivation to use the third intracellular loop.

Applicant argues that it is not reasonable to characterize the substitution of amino acids 171-179 of bacteriorhodopsin with the loop three region from another protein "as routine optimization of operating parameters". Applicant does not appear to provide any arguments to support this assertion. The examiner maintains that the structure of the third loop of bacteriorhodopsin is well known, as evidenced by Popot and Hoflack, and that one of skill in the art would consider it routine to optimize the locations of the cuts in this domain, particularly at positions 171 and 179 as they are specifically defined as forming the third intracellular loop by Teufel et al., in Fig. 2.

Conclusion

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

September 30, 2002

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600